MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Oportunidades en Hepatología

“Poliquistosis hepática”

Agustín Albillos

Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcalá, CIBERehd, Madrid

Caso clínico #1

DIGESTIVO
RAMON Y CAJAL
MADRID

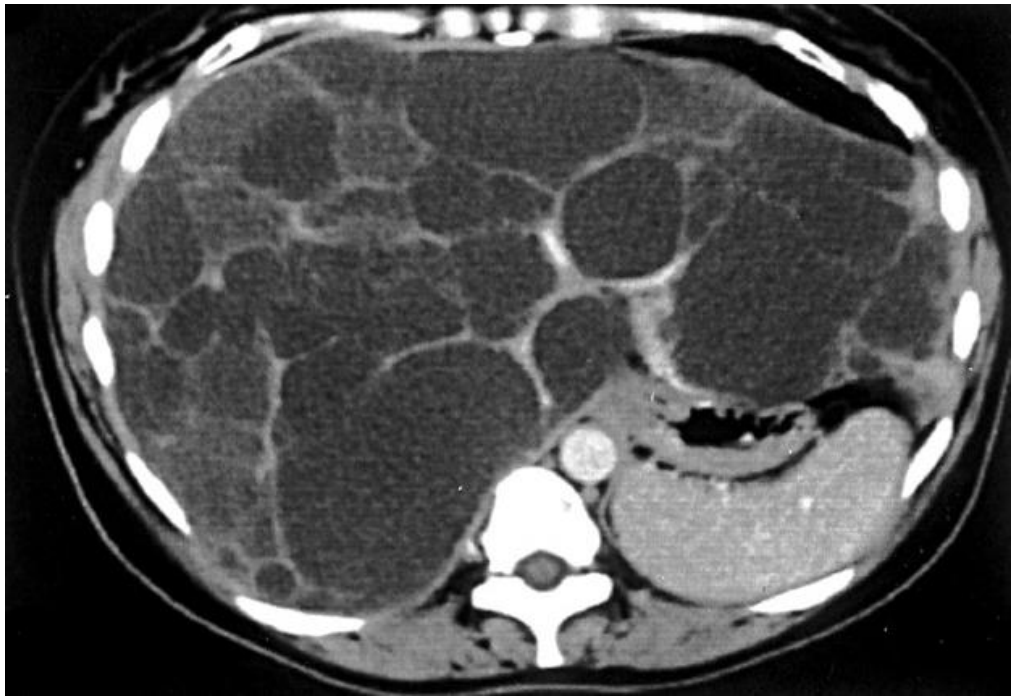
1999 34 años, aumento perímetro abdominal
TAC: múltiples quistes hepáticos y renales
no HTA

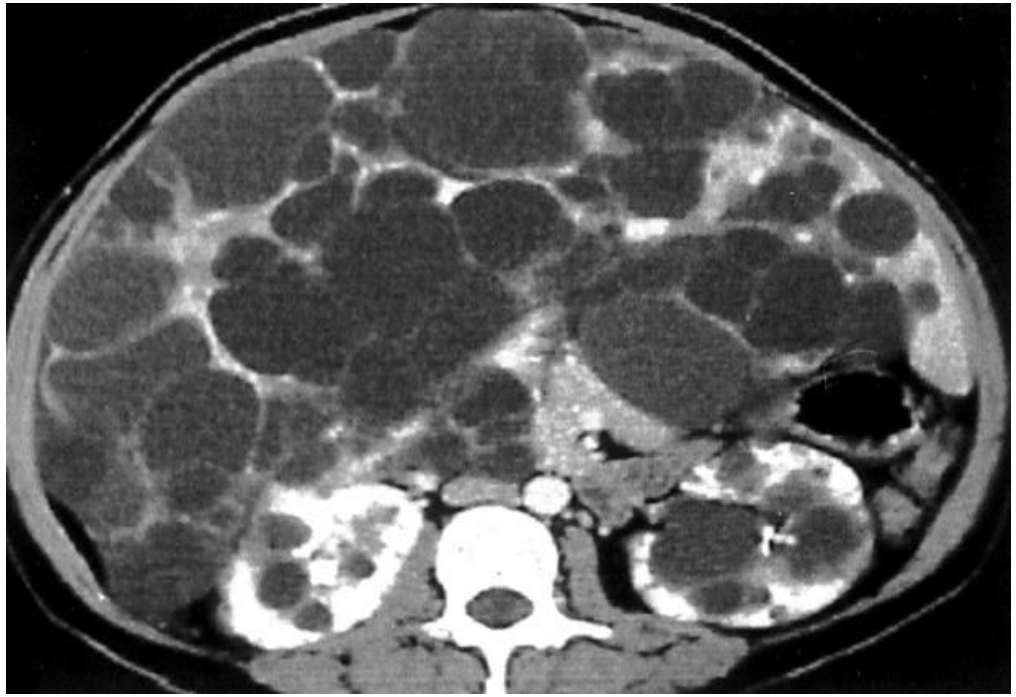
2004 Everolimus durante 1 año sin respuesta

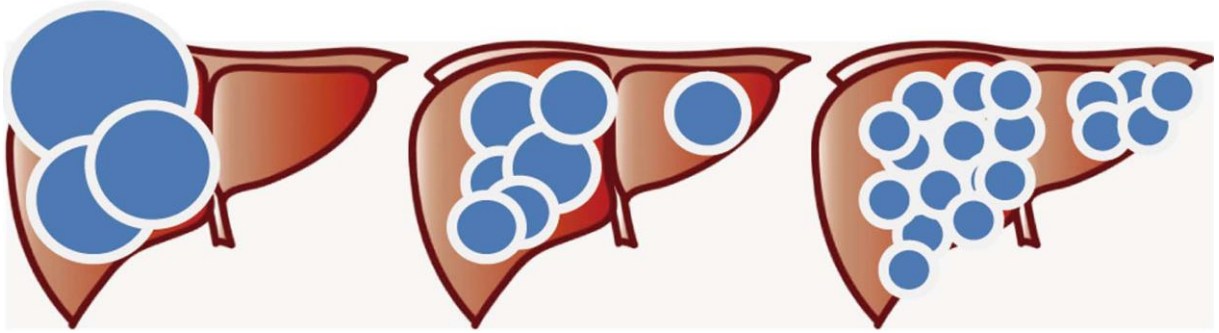
2009 46 años, trasplante hepático por deterioro calidad vida, malnutrición
creat 0.9 mg/dl, albúmina 3.7 g/dl, bili 0.8 mg/dl, GGT 69 UI/ml, FAL 103 UI/ml, INR 1

2009 **Trasplante hepático**
Cirugía: desgarro VCI hasta AD, anastomosis VCI del injerto AD con ligadura VCI del paciente. Injerto 82 años, isquemia fría 10 h
ACVA parietal derecho en postoperatorio por shunt D-I
Alta a los 15 días
Inmunosupresión con tacrolimus y MMF

46 años, massive PLD, mild renal cyst disease, ADPKD
Displacement of the inferior vena cava







Gigot criteria (I-III)

- number and size of the liver cysts
- amount of remaining liver parenchyma
- candidates for fenestration

Gigot I, not PLD (<10 quistes)

Caso clínico #1

DIGESTIVO
RAMON Y CAJAL
MADRID

2017 Hepatología:
FS F4, 17 kPa
Endoscopia oral: varices esofágicas grandes
GPVH 21 mmHg, presión VCI 7 mmHg, no BHT por angulación
Ascitis moderada

Nefrología: ERC estadio 5: poliquistosis, ICN
creat 9.8 mg/dl, hemodiálisis

2020 Riesgo inaceptable retrasplante hepático
albúmina 3.1 g/dl, bili 2.3 mg/dl, INR 1.3
Hemodiálisis 3 veces/sem

Polycystic liver disease (PLD)

DIGESTIVO
RAMON Y CAJAL
MADRID

	ADPLD	ADPKD
Prevalencia	0.01% ~1:100 000	**0.2%** ~1:500-1000
Herencia	AD	AD
Mutaciones	PRKCSH SEC63	PKD1 90% PKD2 10%
Producto codificado	Hepatocistina Mutación SEC-63 (25-40%) ~50% sin PRKCSH/SEC63 mutaciones: más grave	Poliquistina-1 (90%) (más grave) Poliquistina-2 (10%) Fenotipo heterogéneo
Fenotipo	**Quistes hepáticos múltiples** (→ ± renales)	**Quistes renales múltiples** (→ ± hígado 80%) y anomalías vasculares

Natural history and symptoms

DIGESTIVO
RAMON Y CAJAL
MADRID

Natural history of liver cysts

Progressive growing

Prevalence increases with age:

58% at 15-24 yr, **85%** at 25-34 yr, **95%** at 35-46 yr

Growth rate of polycystic livers: 0.9-1.6% in 6-12 m

Severity of liver disease: ADP**L**D with mutations > ADP**L**D > ADP**K**D

Symptoms

80-95% of symptomatic patients and LT ♀, mean age 50 yr

Majority of patients are asymptomatic

Hepatomegaly and symptoms related with liver size

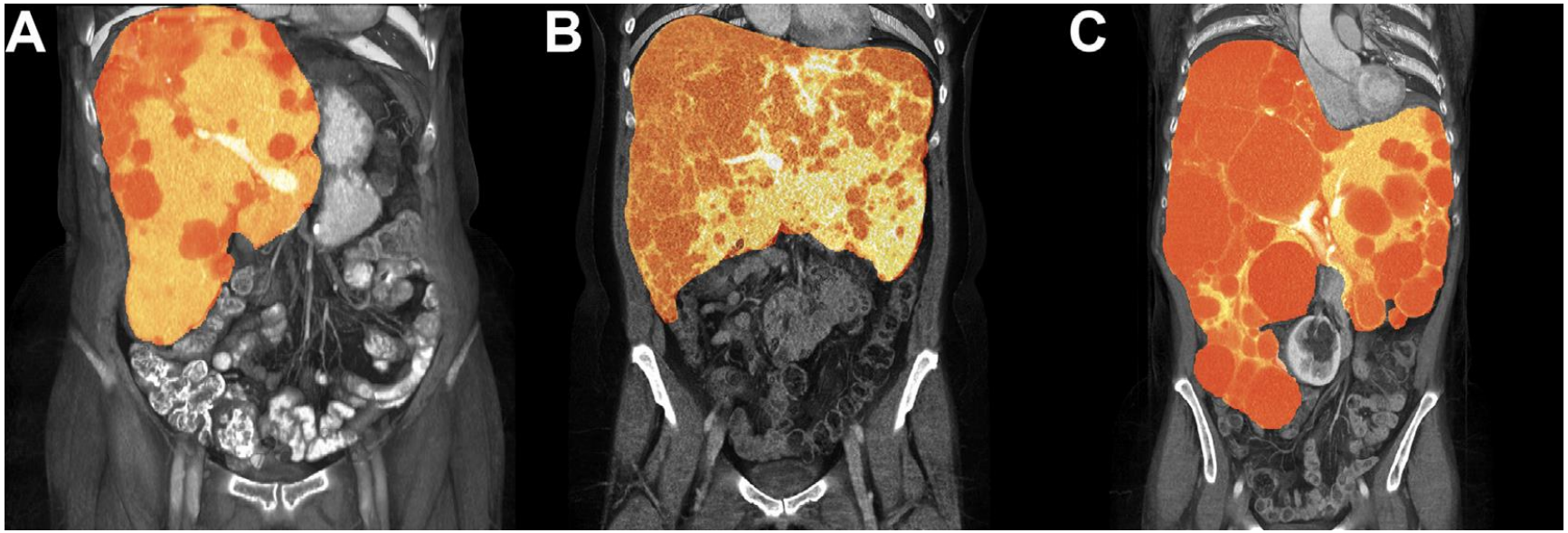
Risk factors for liver cyst growth

- Advancing patient age
- Female gender
- Estrogen exposure: pregnancies, OCPs, estrogen replacement therapy (also in postmenopausal women)
- Severity of renal dysfunction and renal cyst volume

Mild, moderate and severe phenotypes of PLD

htTLV, **height-adjusted total liver volume**

Mild	**Moderate**	**Severe**
<1600 ml/m	1600 - 3200 ml/m	>3200 ml/m



Normal liver volume 1,300–1,700 ml

Natural history and symptoms

DIGESTIVO
RAMON Y CAJAL
MADRID

Complications (rare)

- Cyst infection (punción, In-111 WBC or 67-Gallium scan, PET)
- Cyst bleeding
- Cyst rupture
- Portal hypertension, mostly due to HVOO
- Obstructive jaundice extremely rare

Associated diseases in ADP**K**D (ADPLD?), **systemic disease**

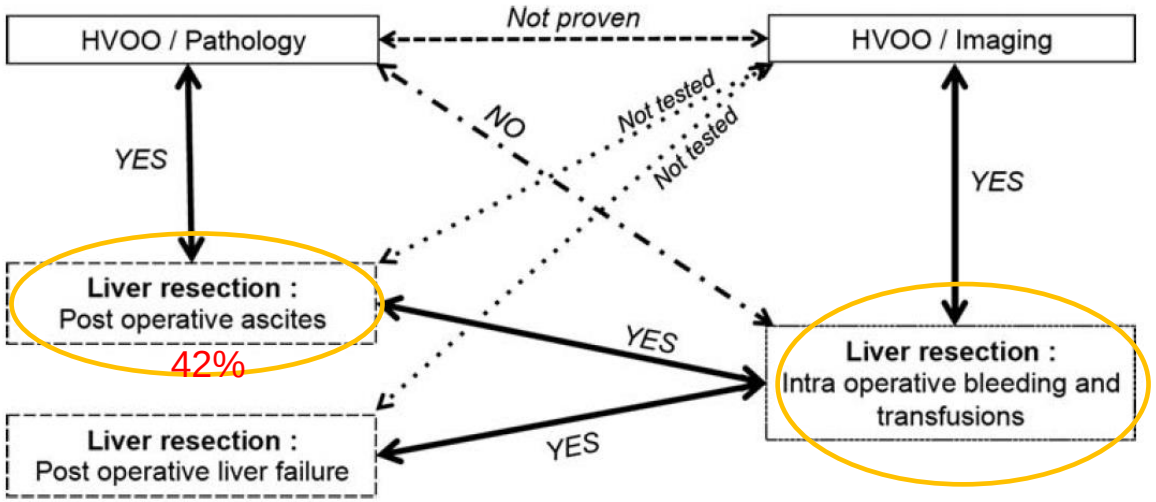
- Pancreatic cysts (10%)
- Arachnoid cysts
- Intracranial aneurysms, 16% and 6% with or w/o family history
  Screening: >30 yr, symptoms, family history (aneurysms, stroke),
  LTx/KTx candidate
- Valvular disease: mitral valve prolapse (25%), aortic regurgitation (10%)
- Arterial hypertension, 70%, <u>even before</u> KD (ADKPD)
- Left ventricular hypertrophy
- <u>NOT</u> increased risk of malignancy

Hepatic venous outflow obstruction in polycystic liver disease

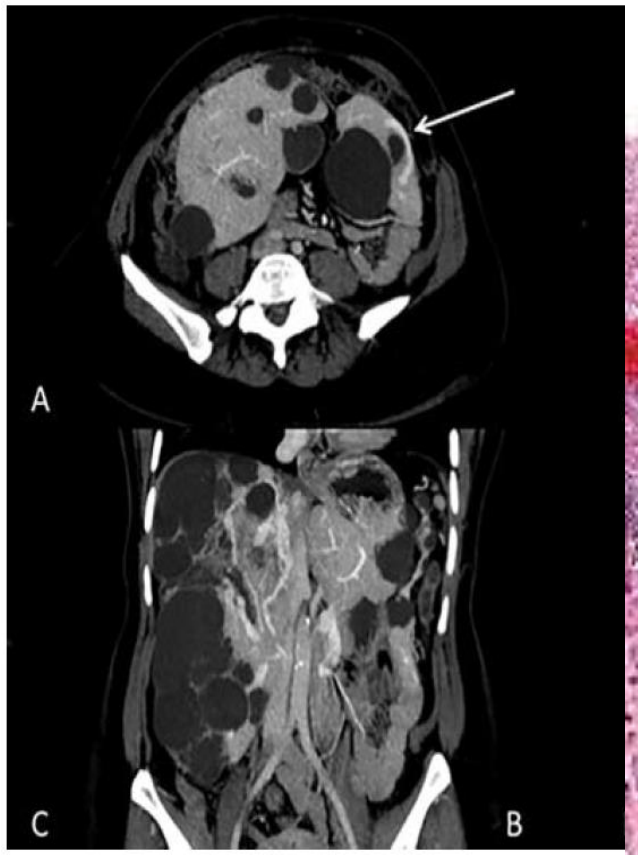
DIGESTIVO RAMON Y CAJAL MADRID

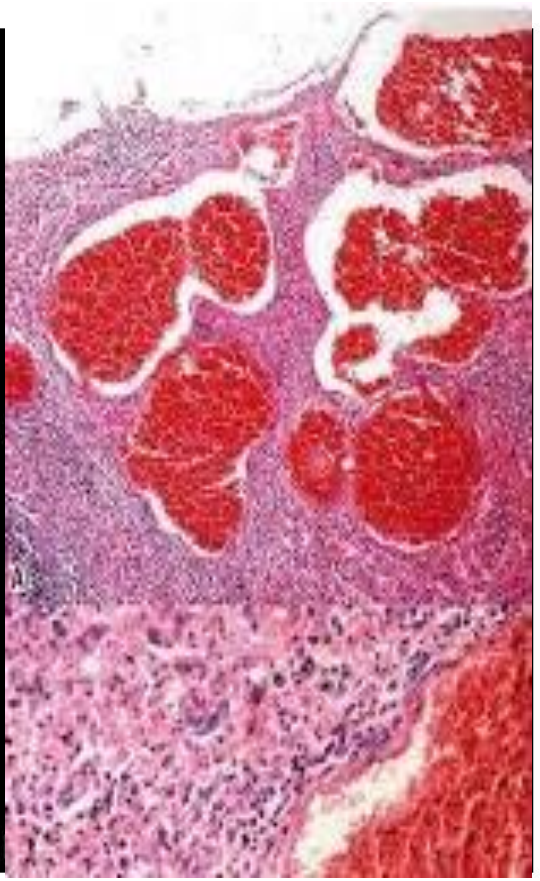
Retrospective study of **125 patients with ADPLD**
90 resection, 35 LT

Histology (n=125)	Imaging TC (n=45)
92% lesions of HVOO (47% sinusoidal dilatation) **Fibrosis 57%** (advanced 13%)	100% stenosis/obstruction 2 HV 87% 3 HV affected 84% intrahepatic collaterals



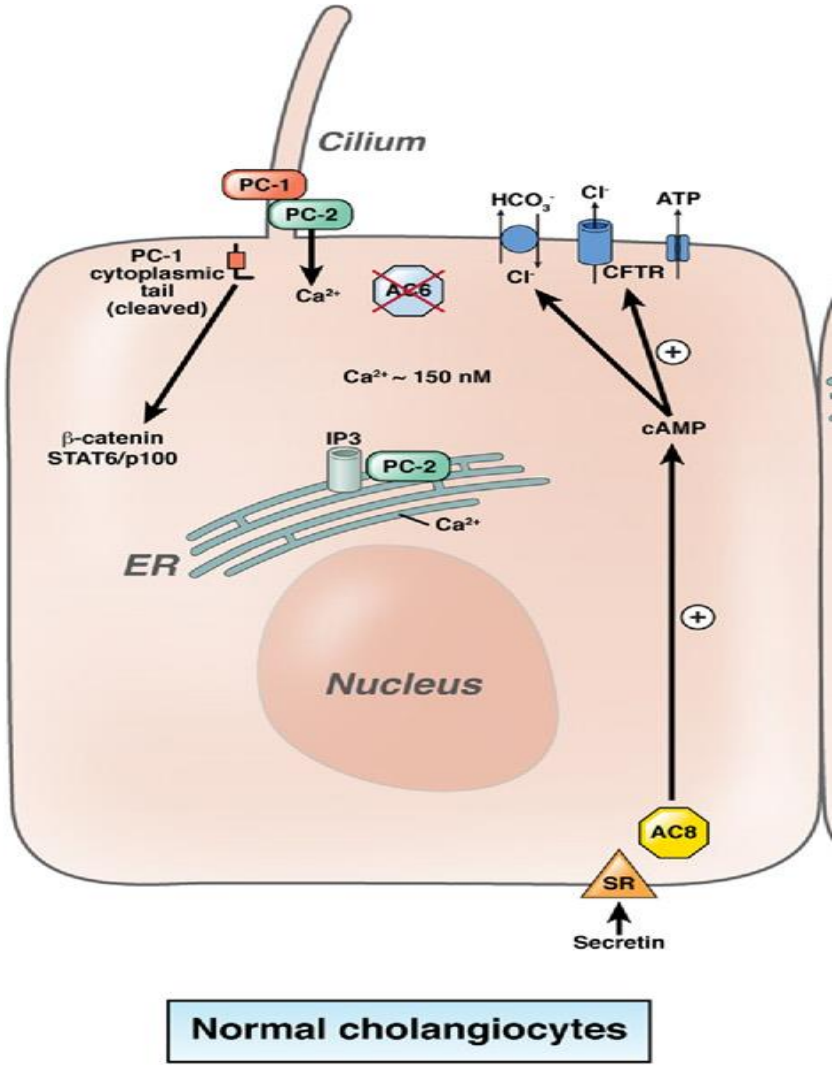
HVOO lesions: sinusoidal dilatation, congestion, peliosis, nodular regenerative hyperplasia





Barbier L et al. Hepatology 2018

Signaling in normal and cyst cholangiocytes



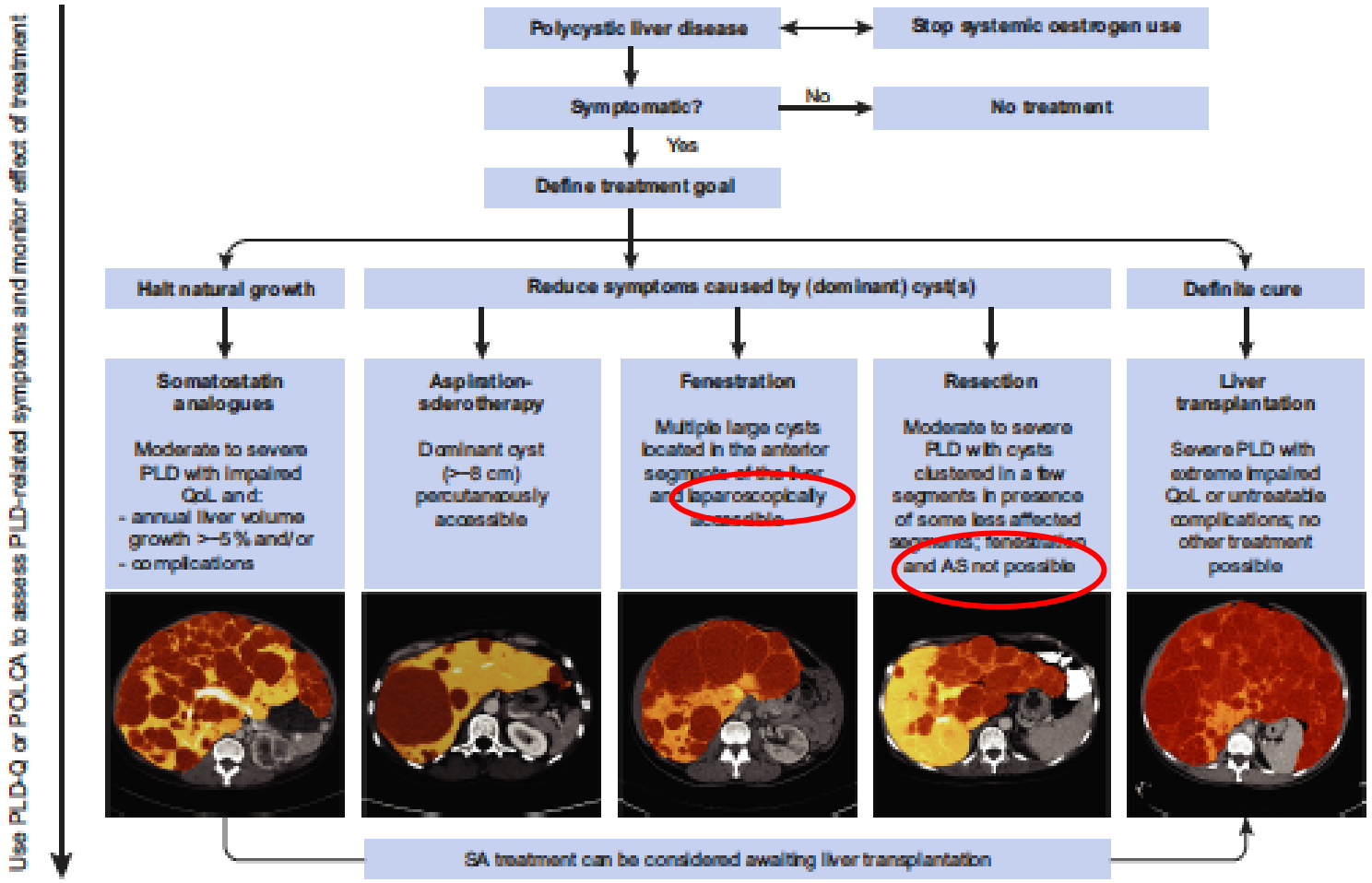
Normal cholangiocytes

Phenotypic changes in cyst cholagiocytes

- Less differentiated phenotype
- ↑ cAMP levels
  (drive fluid secretion and proliferation)
- ↑ proliferation/apoptosis
- ↑VEGF and VEGFR2 expression
- ↑ cytokines and chemokines expression
- ↓ cytoplasmic [Ca^{2+}]
- ↑ expression of mTOR, pERK1/2
- Changes in ER functions

M Strazzabosco et al. Gastroenterology 2011

Treatment algorithm for polycystic liver disease



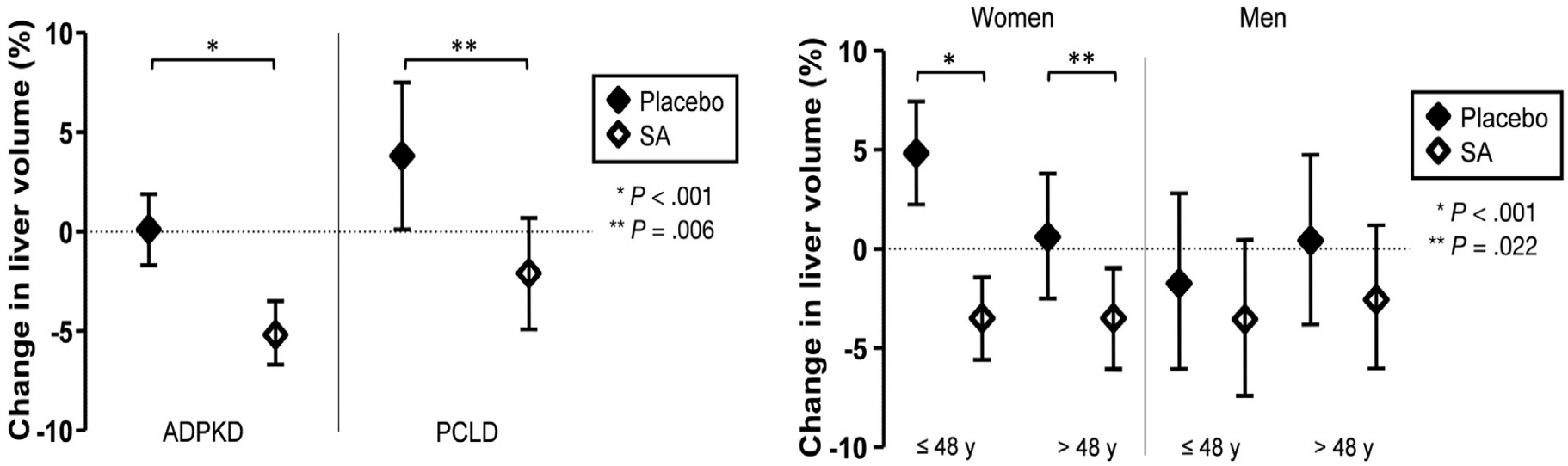
R van Aerts et al. *JHEP 2018*

Young women with Polycystic Liver Disease respond best to somatostatin analogues: A Pooled Analysis of Individual Patient Data

DIGESTIVO RAMON Y CAJAL MADRID

Primary outcome: change in liver volume after 6-12 m

Lanreotide 120 mg/4 wks sc / **Octreotide** 40 mg/4 wks sc



- Heterogeneity in response: 15% non-response
- Underlying diagnosis**: little influence**
- **Young women** (<48 yr) largest increase in liver volume, best response
- Ineffective in men, modestly effective in older women
- ~~Treatment beyond 24 m little benefit. Once stopped, liver volume rebounds~~
- ~~No effect on kidney volume~~
- **Target population:** women with extensive PLD and symptoms

TG Gevers et al. Gastroenterology 2013

Lanreotide reduces liver growth in patients with autosomal dominant polycystic liver and kidney disease

DIGESTIVO RAMON Y CAJAL MADRID

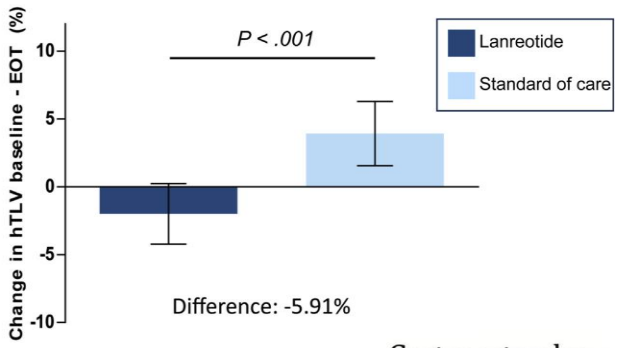
A 120-week randomized clinical trial

Autosomal Dominant Polycystic Kidney and Liver Disease patients with liver volume ≥ 2000mL

Lanreotide 120 mg sc every 28 days

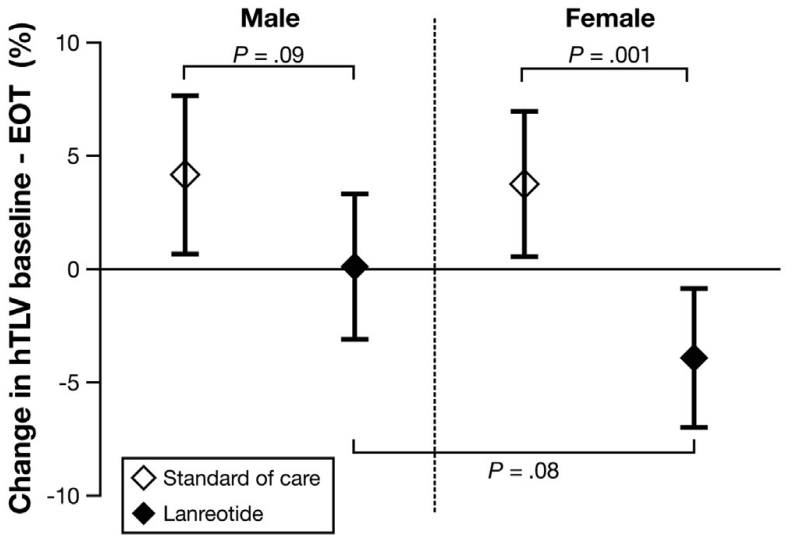
Standard of care

Primary outcome
% change in height adjusted total liver volume (hTLV) from baseline to end of treatment (EOT)

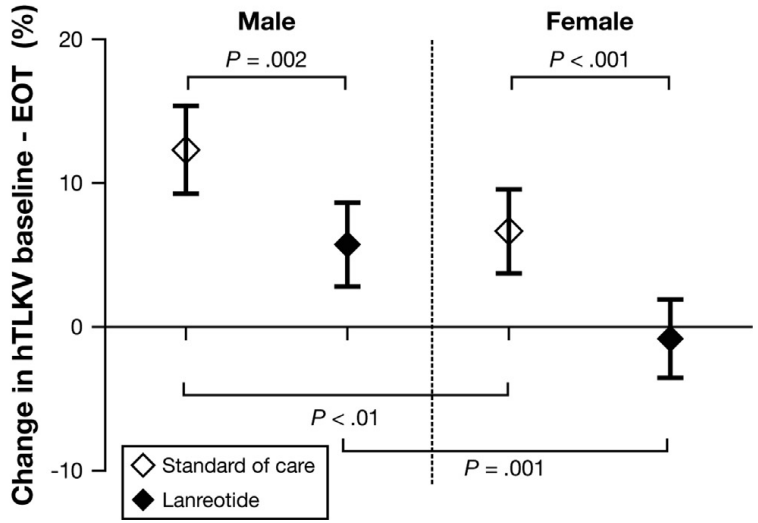


Gastroenterology

hTLV at the end of treatment



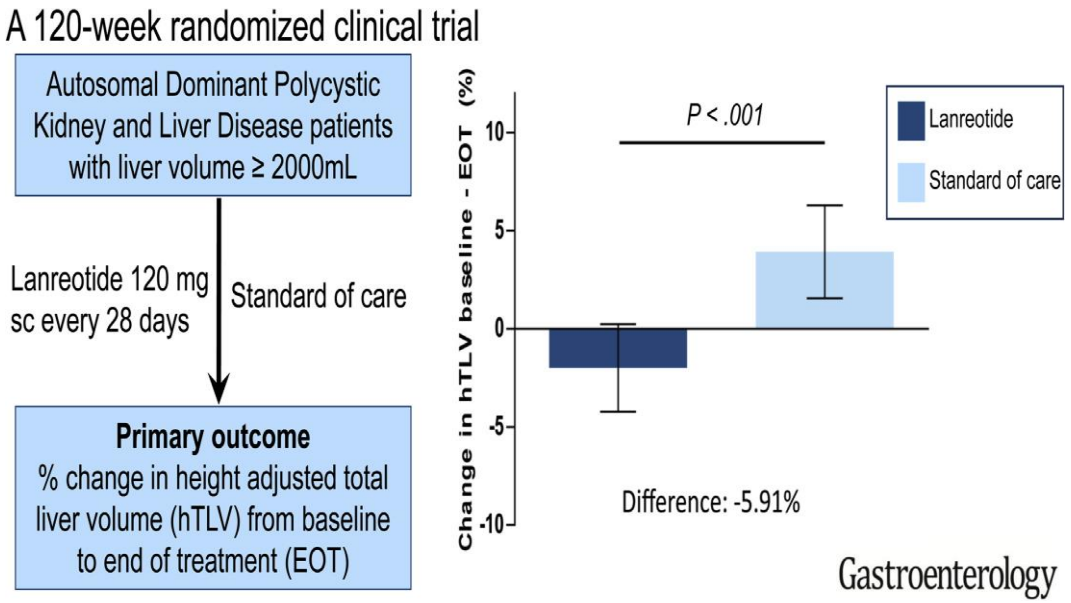
hTLKV at the end of treatment



hTLV still reduced by 3.87% at 4 months after last injection of lanreotide (P .04)

RM van Aerts et al. Gastroenterology 2019

Lanreotide reduces liver growth in patients with autosomal dominant polycystic liver and kidney disease



Adverse events

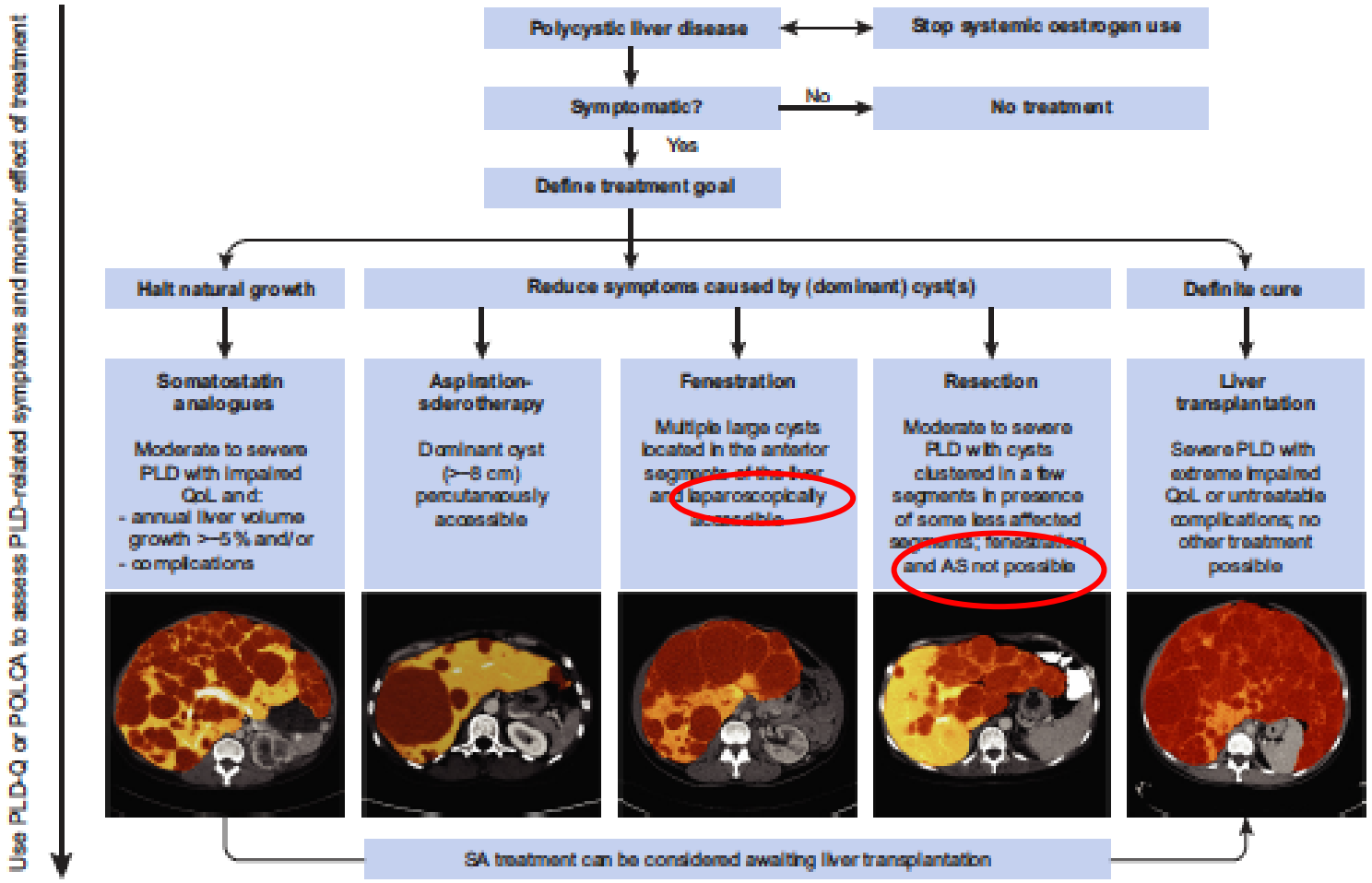
- 15/93 (16%) patients dose reduction, 6 stopped (7 GI complains, 3 malaise, 2 bradycardia, 1 hypoglycemia, 1 hair loss, 1 cyst infection)
- **6 liver cyst infection**

Limitations

- No change in QoL
- Most w/o hepatomegaly-related complains (hTLV >3200 ml/m)(14% LAR, 6% SOC)

RM van Aerts et al. Gastroenterology 2019

Treatment algorithm for polycystic liver disease

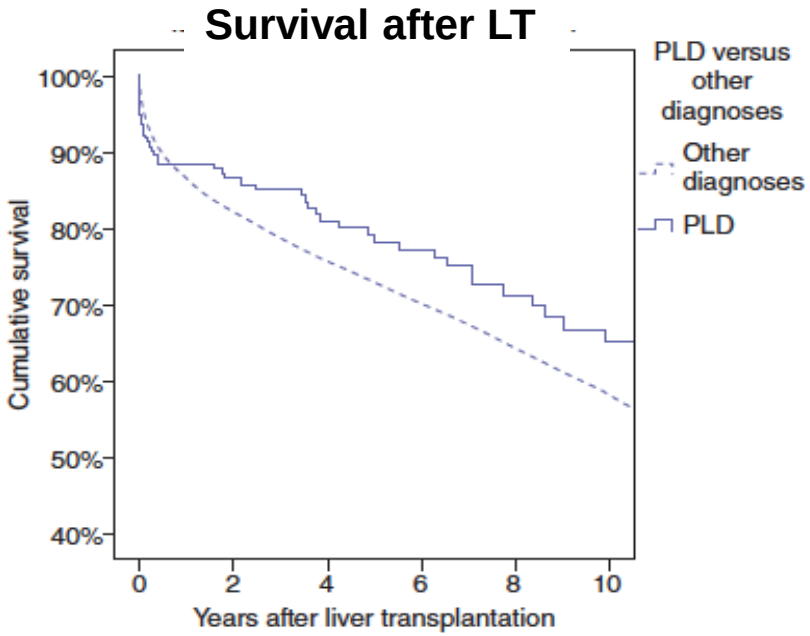


R van Aerts et al. *JHEP 2018*

Liver transplantation in polycystic liver disease

DIGESTIVO
RAMON Y CAJAL
MADRID

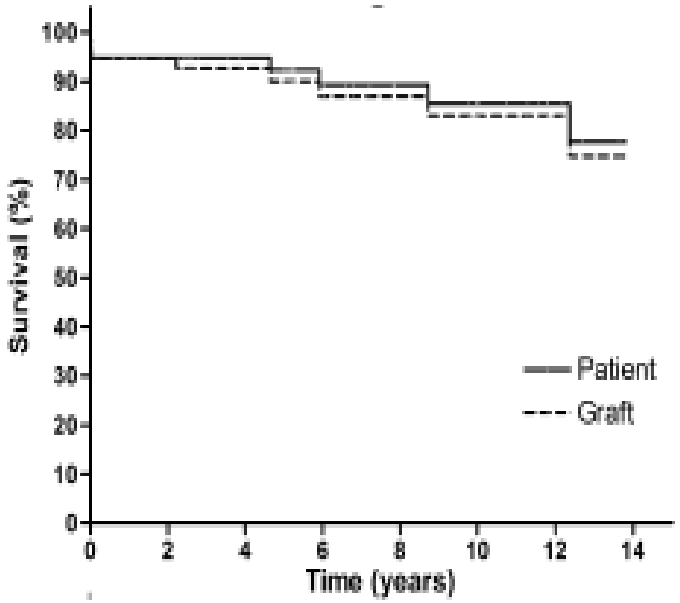
Retrospective UNOS database
107 411 LT (**1988-2010**) → 0.3% PLD



30-day mortality (1-survival)	<1 January 2000	≥1 January 2000	Wilcoxon's *P*-value
PLD	12% (*n* = 122)	7% (*n* = 235)	0.038
Other transplants	8% (*n* = 3520)	5% (*n* = 5782)	<0.001

Gedaly R et al. *HPB Surg* 2013

Retrospective **ELTR** database
58 PLD, **1985-2007**



Reasons for LT
- 74% mechanical difficulties
- 14% pain
- 12% complications

Difficulties in surgery, 38%
- 17% prior surgery!!
- 12% grossly enlarged liver

Keimpema L et al. *Transplant Int* 2011

Liver transplantation in polycystic liver disease

DIGESTIVO
RAMON Y CAJAL
MADRID

Criteria for LT

- massive PLD with symptoms
(exceptional *hTLV <5000 ml/m*)
- severe malnutrition
(albumin <2.2 g/dl)
- portal hypertension, including HVOO
- recurrent cyst infection

MELD exception

• w/o renal insufficiency, GFR >30 ml/min, MELD 15 (plus 3 points/3 mo)
• with renal insufficiency, GFR <30 ml/min, MELD 20 (plus 3 points/3 mo.)

Arrazola L et al. *Liver Transplant*. 2006

Ethical issues

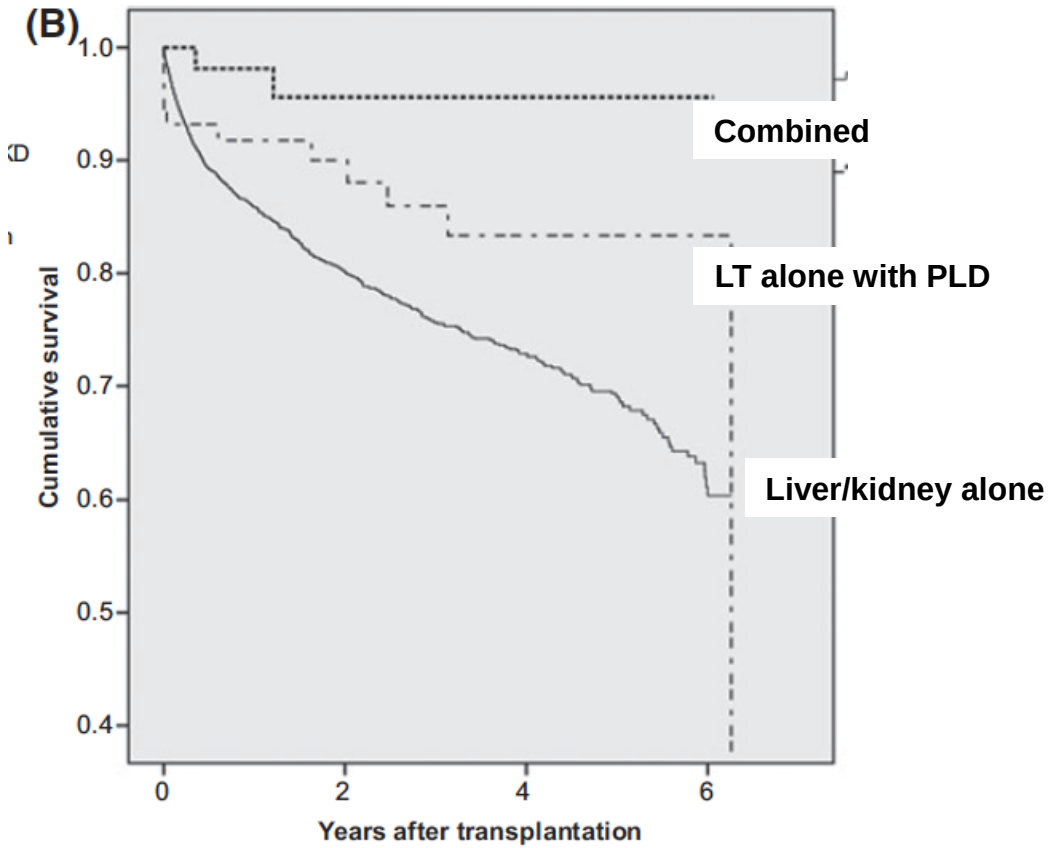
UNOS database 2002-15
>70% more likely transplanted than cirrhosis

SD Doshi et al. Transplantation 2017

Combined liver/kidney transplantation in polycystic liver disease

DIGESTIVO RAMON Y CAJAL MADRID

Survival after LT



Retrospective UNOS database
107 411 LT (**1988-2013**) → 107 liver/kidney T

	1-Year	3-Year	5-Year
	Patient survival	Patient survival	Patient survival
PLD/PKD	91%	90%	90%
PLD alone	87%	82%	77%
Other liver–kidney	82%	73%	67%

C Coquillard et al. *Liver Int 2016*

Key points

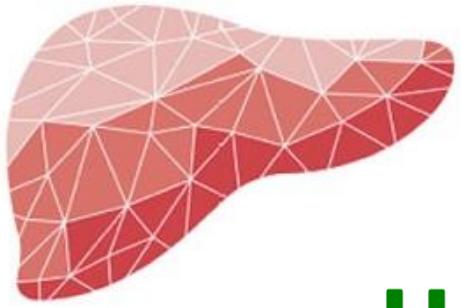
— Cyst growth depends of female sex and age

— Hepatic vein outflow obstruction is common in massive PLD

— Young women with symptomatic disease are the target of somatostatin analogues

— Increased mortality of LT at short-term

MÁSTER EN HEPATOLOGÍA



UAM
Universidad Autónoma de Madrid

Universidad de Alcalá